



# **The IDEA (International Duration Evaluation of Adjuvant Chemotherapy) Collaboration: Prospective Combined Analysis of Phase III Trials Investigating Duration of Adjuvant Therapy with the FOLFOX (FOLFOX4 or Modified FOLFOX6) or XELOX (3 versus 6 months) Regimen for Patients with Stage III Colon Cancer: Trial Design and Current Status**

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# The IDEA (International Duration Evaluation of Adjuvant Chemotherapy) Collaboration: Prospective Combined Analysis of Phase III Trials Investigating Duration of Adjuvant Therapy with the FOLFOX (FOLFOX4 or Modified FOLFOX6) or XELOX (3 versus 6 months) Regimen for Patients with Stage III Colon Cancer: Trial Design and Current Status

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for the IDEA Steering Committee

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**Abstract** The International Duration Evaluation of Adjuvant Chemotherapy (IDEA) collaboration was established to prospectively combine and analyze data from several randomized trials conducted around the world to answer whether a three-month course of oxaliplatin-based adjuvant therapy (FOLFOX4/modified FOLFOX6 or XELOX) is non-inferior to the current standard six-month treatment for

patients with stage III colon cancer, with a primary endpoint of three years disease-free survival. The IDEA steering committee comprises two members from each group coordinating an individual trial and two members from a secretariat who coordinate combining of the data and management of the joint analysis. Members of the IDEA agreed to combine the data from their individual trials to enable definitive

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**IDEA Steering Committee:** Timothy Iveson, M.D. and James Paul, B.Sc., Short Course Oncology Treatment (SCOT) trial; Cancer Clinical Trials Unit Scotland (CACTUS) and Oncology Clinical Trials Office (OCTO) groups

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analysis consisting of at least 10,500 patients. With accrual of 8,797 patients at the end of February 2013, the IDEA is on track to achieve its accrual objective of at least 10,500 patients by the end of 2013.

**Keywords** Colon cancer · Colonic neoplasms · Adjuvants pharmaceutical · Stage III · Chemotherapy · Fluoropyrimidines · 5-Fluorouracil · Leucovorin · Oxaliplatin · Capecitabine · Phase III · Duration of therapy · Neuropathy · International collaboration

## Introduction

Six months of adjuvant chemotherapy with fluoropyrimidines (5-fluorouracil and leucovorin (5-FU/LV) or capecitabine) and oxaliplatin is the current worldwide standard of care for patients with stage III colon cancer, based on the findings from three large trials—the Multicenter International Study of Oxaliplatin/5-FU/LV in the Adjuvant Treatment of Colon Cancer (MOSAIC), the National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07 trial, and the NO16968 study [1, 2•, 3, 4•, 5•, 6].

The MOSAIC randomized phase III trial compared the efficacy of 5-FU/LV in combination with oxaliplatin (FOLFOX4 regimen) with that of 5-FU/LV, for six months, among patients with stage II and III colon cancer [1, 2•]. A 24 % (HR=0.76,  $p=0.005$ ) reduction in relative risk of relapse was observed among stage III patients receiving FOLFOX4. The updated results, published in 2009, revealed an advantage in terms of five-year disease-free survival (DFS) for FOLFOX4 (66.4 %) over 5-FU/LV (58.9 %; HR=0.78,  $p=0.005$ ) among patients with stage III colon cancer. Six-year overall survival (OS) was 72.9 % for patients receiving

FOLFOX4 compared with 68.7 % for patients in the control group (HR=0.80,  $p=0.023$ ) [1, 2•]. The NSABP C-07 trial compared the efficacy of oxaliplatin added to a weekly bolus 5-FU/LV regimen (FLOX) with that of bolus 5-FU/LV alone (Roswell Park regimen). This study revealed a benefit of oxaliplatin addition for stage III patients: five-year DFS was 64.4 % vs. 57.8 % ( $p<0.0007$ ) and five-year OS was 76.5 % vs. 73.8 %, HR=0.85 ( $p=0.052$ ) [3, 4•]. A third study, the NO16968 trial, compared a three-weekly capecitabine and oxaliplatin regimen (XELOX) versus bolus 5-FU/LV (Mayo Clinic or Roswell Park regimen) for stage III colon cancer and showed a three-year DFS of 70.9 % with XELOX vs. 66.5 % with 5-FU/LV (HR=0.80,  $p=0.0045$ ). Similarly, a significant improvement associated with XELOX on OS at seven years was observed (73 % vs. 67 %, HR=0.83,  $p=0.0367$ ) [5•, 6]. Results from these three positive adjuvant phase III trials supported the survival benefit of adding oxaliplatin to fluoropyrimidines in the adjuvant setting for patients with stage III colon cancer [1, 2•, 3, 4•, 5•, 6].

Despite the efficacy of fluoropyrimidines and oxaliplatin-based chemotherapy for patients with stage III colon cancer, this treatment leads to significant cost, toxicity, and patient inconvenience. In particular, oxaliplatin-induced cumulative dose-dependent neurotoxicity is clinically relevant. In the MOSAIC trial, the incidence of grade 3 neurotoxicity one year after completion of treatment was estimated to be 12 %, and grade 1 or 2 neurotoxicity in the second post-treatment year was still affecting approximately 50 % of patients [1, 2•].

In colon cancer the initial demonstration of efficacy of adjuvant 5-FU plus levamisole was based upon 12 months of treatment [7]. Thereafter, 6 months of 5-FU/LV proved to be as effective as 12 months of 5-FU/levamisole. Subsequent studies of the Intergroup trial 0089 (INT-0089) supported equivalence of 6 months 5-FU/LV adjuvant chemotherapy and 12 months 5-FU/levamisole treatment [8]. Furthermore, the Groupe Cooperateur Multidisciplinaire en Oncologie (GERCOR) trial showed that 6 months of the 5-FU/LV regimen is as effective as 9 months of 5-FU/LV in the adjuvant setting [9, 10].

Chau et al., conducted an adjuvant treatment trial of 801 patients with stage II and III colorectal cancer, and demonstrated that three months of protracted venous infusion of 5-FU is as effective as six months of standard bolus 5-FU/LV and significantly less toxic [11]. Although the study was designed as a superiority trial, the analysis conducted concluded that the chances of the three-month regimen being inferior to the six-month treatment plan were extremely low ( $p<0.005$ ). No other study has investigated the possibility of further reducing the duration of the entire adjuvant chemotherapy below six months for patients with stage III colon cancer. More recent data, however, provide additional arguments supporting the plausibility of shorter duration treatment without loss of efficacy.

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Two studies, the MOSAIC and NSABP C-07, provided evidence in support of changing to shorter-duration FOLFOX doublet-based treatment. In those two studies, the benefit of six months FOLFOX treatment (MOSAIC) was identical with that of FLOX regimen (NSABP C-07); the total dose of oxaliplatin in the two studies differed by approximately 30 %. Moreover, whereas the per-protocol planned oxaliplatin dose was 1,020 mg/m<sup>2</sup> (12 cycles) in MOSAIC and 765 mg/m<sup>2</sup> (nine cycles) in C-07, the median oxaliplatin dose received per-patient was 810 mg/m<sup>2</sup> (9.5 cycles) and 667 mg/m<sup>2</sup> (7.8 cycles) in MOSAIC and C-07, respectively [1, 2•, 3, 4•].

In addition, a recent study of 2,560 colon cancer patients who received adjuvant fluoropyrimidine and oxaliplatin adjuvant therapy between January 2004 and April 2010 at US cancer care facilities participating in a nationwide, commercially available chemotherapy order entry system showed that 26.9 % of patients did not complete more than three months of therapy [12].

The ability to maintain the efficacy of treatment with a reduced duration of therapy would clearly be advantageous to patients, health care providers, and health care systems. To eliminate the possibility of clinically meaningful inferiority of three months of therapy a large number of patients will be necessary. Previous efforts and experience have conclusively demonstrated that for colon cancer, a single, global trial is impractical for answering the question of the duration of adjuvant chemotherapy. Consequently, independent trials worldwide are currently in progress to gather data and perform a prospective combined analysis to answer the single primary hypothesis that 3 months of adjuvant therapy with oxaliplatin-based chemotherapy is non-inferior to the current standard of six months for patients with stage III colon cancer.

## Methods

To be included in the IDEA combined analysis all trials must share a limited number of characteristics. Specific requirements include:

- enrolment of patients with stage III colon cancer;
- randomization of patients into a standard group with a planned 12 treatments of FOLFOX (FOLFOX4 or modified FOLFOX6 (mFOLFOX6)) or eight treatments of XELOX and an experimental group with planned six treatments of FOLFOX (FOLFOX4 or mFOLFOX6) or four cycles of XELOX;
- use of DFS at three years as primary endpoint;
- optimum stratification (recommended and optional) of patients by clinical T-stage (T1/T2 vs. T3 vs. T4), performance status (PS, 0 vs. 1 vs. 2), and age (<70 vs. ≥70); and
- agreement of the investigators to combine data for the IDEA definitive analysis.

Each individual trial may contain additional, trial-specific hypotheses in a factorial design, and may include other trial-specific secondary aims, for example translational, quality of life, health economic, and others. Finally, each trial may also enable enrolment of patients with stage II colon cancer or rectal cancer, but the IDEA combined analysis will consist only of patients with stage III colon cancer enrolled in these trials. To the extent possible, every effort will be made to keep all trials included in IDEA as simple as possible in terms of eligibility criteria and data collection. However, except for a limited number of mandatory data items (Table 1), information on individual trial follow-up and data collection will be specific to each trial.

The following six trials are currently participating in the IDEA project:

- the Italian Three or Six Colon Adjuvant (TOSCA) trial;
- the UK Short Course Oncology Treatment (SCOT) trial;
- the IDEA France trial;
- the intergroup Cancer and Leukemia Group B/Southwest Oncology Group (CALGB/SWOG) trial 80702;
- the Greek Hellenic Oncology Research Group (HORG) trial; and
- the Japanese Adjuvant Chemotherapy for colon cancer with High EvidencE (ACHIEVE) trial.

Four of these trials, the SCOT, IDEA France, Japanese ACHIEVE, and HORG are addressing the single question of the noninferiority of three months of oxaliplatin-based adjuvant chemotherapy versus the current standard of six months. The Italian TOSCA trial, in addition to the primary question in its factorial design, also initially assessed whether the combination of bevacizumab with FOLFOX4 is superior to FOLFOX4 alone. The TOSCA randomization of bevacizumab was closed after publication of results from the NSABP C-08 study [13•]. The US Intergroup 80702 colon trial, in addition to randomization of three versus six months, randomizes patients to three years of celecoxib or placebo, both in combination with mFOLFOX6, in a 2×2 factorial design. The trial will test for superiority in DFS of celecoxib compared with placebo. The IDEA collaboration will not report its primary findings until all six included trials have completed their accrual.

## Chemotherapy

### FOLFOX4

A two-hour infusion of LV 200 mg/m<sup>2</sup> followed by a 400 mg/m<sup>2</sup> bolus 5-FU followed by a 22-hour infusion of 5-FU 600 mg/m<sup>2</sup> given on two consecutive days plus a two-hour infusion of 85 mg/m<sup>2</sup> oxaliplatin, on day 1, simultaneously with LV, using a Y-infusion device.

## mFOLFOX6

Oxaliplatin 85 mg/m<sup>2</sup> intravenous (IV) infusion with LV 400 mg/m<sup>2</sup> over two hours using a Y-infusion device, followed by 400 mg/m<sup>2</sup> bolus 5-FU followed by an IV infusion of 5-FU 2400 mg/m<sup>2</sup> for 46 hours. (N.B. In the SCOT trial, the dose of LV is fixed to 350 mg total dose.)

## XELOX

Oxaliplatin 130 mg/m<sup>2</sup> IV infusion over two hours (day 1 every three weeks) in combination with capecitabine administered orally at a dose of 1000 mg/m<sup>2</sup> twice-daily (equivalent to a total daily dose of 2000 mg/m<sup>2</sup>, the first evening dose on day 1 and the last morning dose on day 15) given as intermittent treatment (three-week cycles consisting of two weeks of treatment followed by one week without treatment).

Dose modification as a result of adverse events and toxicity is being conducted on the basis of standard clinical practice unless specified in the individual protocols.

## Data sharing

Data transfer from each individual trial to the IDEA database will be coordinated individually with each trial on the basis of local data-transfer restrictions and requirements. It is expected that at least one annual report on the number of DFS events in the two groups will be submitted to IDEA to facilitate interim analysis. To ensure data quality, and to monitor the number of DFS events for the interim analysis, records (exclusively de-identified data) from each individual trial will be electronically transmitted to the IDEA secretariat. When the primary analysis has been completed, a de-identified dataset from the primary analysis will be made available to all IDEA members. Each individual group will be authorized to include or exclude their data from any subsequent analysis proposed by IDEA members. The data required for the IDEA combined analysis are included in Table 1.

## IDEA Steering Committee

The IDEA steering committee comprises two members from each group coordinating an individual trial with two members from a secretariat who will be responsible for coordinating combination of the data and the joint analysis. It is expected that the IDEA secretariat will be independent of any of the groups that are leading the individual trials.

**Table 1** Required data elements for the IDEA trials

<i>Baseline data</i>
Age in years at randomization (date of birth)
Baseline performance status
Sex (M/F)
Number of nodes positive/number of nodes examined
T stage (1, 2, 3, 4)
Obstruction (Y/N); perforation (Y/N)
Adherence (Y/N)
Histology: high grade (not or slightly differentiated)/low grade (moderately or well differentiated)
Date of surgery, date of randomization
Eligibility status (Y/N)
Randomization group (3 or 6 months)
Ancillary randomization arm (if a 2×2 factorial design)
<i>Treatment data</i>
Date of first cycle of adjuvant treatment, date of last adjuvant cycle
Total number of two-week cycles delivered, total FU dose (in mg/m <sup>2</sup> ), Total oxaliplatin dose (in mg/m <sup>2</sup> )
Calcium and magnesium (Y/N)
Reason treatment protocol ended (completion per protocol, adverse event, patient refusal, recurrence, other)
<i>Adverse event data: worst grade experienced during the on-study period (up to one month after last administration of chemotherapy):</i>
Neutropenia (0 to 5), thrombocytopenia (0 to 5)
Diarrhea (0 to 5), nausea (0 to 5), vomiting (0 to 5)
Stomatitis (0 to 5)
Fatigue (0 to 5)
Neuropathy (0 to 4)—worst grade during or just after study chemotherapy, i.e. within one month after the end of chemotherapy
Febrile neutropenia (0 to 5)
Allergy (0 to 5), other, specify (0 to 5)
<i>Follow-up data (at each follow-up visit)</i>
Date of follow-up visit neuropathy (Y/N, if yes, grade)
Recurrence status (Y/N)
If recurrence, date and site of recurrence
Vital status (Y/N)
If dead, date of death
If dead, cause of death (this cancer, other cancer, other, unknown)
Other second primary cancer (Y/N) – If yes, location.

## IDEA Data and Safety Monitoring Board (DSMB)

The committee agreed to the establishment of an IDEA DSMB to consider the results of the interim analysis. The committee will review efficacy data only, because tolerability is not relevant for the standard of care treatment. The IDEA DSMB membership is composed of four members: the chairs of the DSMBs of the TOSCA, SCOT, and CALGB/SWOG trials, and a statistician. The IDEA DSMB will consider the confidential results of the interim analysis and report the blinded outcome to



the IDEA steering committee. The IDEA Secretariat will contract with an independent statistician to perform the analysis for the IDEA DSMB.

## Statistics

The primary efficacy variable for the IDEA combined analysis is DFS at three years, defined as the time from randomization to relapse or death, whichever occurred first. Second colorectal cancers are regarded as DFS events, whereas non-colorectal tumors are to be disregarded in the analysis.

The objective of IDEA is to combine data from several clinical trials, each with individual planned sample sizes of a minimum of 1000 patients, to ensure success in achieving at least 10,500 patients for the combined analysis.

The IDEA primary efficacy analysis will estimate the hazard ratio for DFS comparing three with six months of therapy using a Cox proportional hazards regression model. As originally planned, noninferiority was to be declared if the two-sided 95 % confidence interval for the hazard ratio comparing three to six months of therapy lies entirely below 1.10. Individual IDEA trials may also address additional study-specific hypotheses; to protect the integrity of each individual trial, however, these will not be included in the IDEA analysis. The primary analysis will be modified intention to treat, including patients in their randomized group, irrespective of the actual treatment or duration of treatment received, with only patients who receive no therapy whatsoever excluded from the analysis. This is to avoid the potential bias of a conventional per-protocol analysis, which may be typically considered for a noninferiority trial, in that patients in the six month group who complete three or fewer months of therapy may be a biased sub-group to include with patients randomized to the three month arm as would be done in a per-protocol analysis. Secondary analysis, however, will investigate the effects of compliance with treatment duration. A sample size of 10,500 patients provides 90 % power, based on expected accrual duration of 3.5 years, three years minimum follow-up, and expected three-year DFS in the control group of 72 %. Given that this is a noninferiority trial and there is no expectation of superior results for the reduced duration therapy, an interim analysis to conclude noninferiority

will not be conducted. Two interim analyses for inferiority of three months of therapy, at 50 % and 75 % of the protocol-specified combined number of events, were initially planned.

## IDEA Updates

After IDEA Steering Committee discussions in January 2013 at the American Society of Clinical Oncology (ASCO) Gastrointestinal (GI) Symposium (San Francisco, California, USA) two major decisions were reached.

### IDEA analysis plan modification

The committee discussed extensively the need for a revised analysis plan for IDEA, because of the expectation of fewer events than planned after three years of follow-up. In the IDEA design, the critical driver of the analysis timing is the number of DFS events, given that the precise accrual and follow-up patterns will differ among the six included studies. The initial primary IDEA hypothesis was based on two contemporary trials, MOSAIC, and NSAPB C07. In these studies, the number of DFS events after three years has subsequently been demonstrated to be low (Table 2). In addition, in recent studies, DFS at three years with FOLFOX4 or mFOLFOX6 has been superior to the assumed 72 % DFS at three years for six months of FOLFOX or XELOX (Table 2) [1, 2•, 3, 4•, 5•, 6]. As a result, it became clear that the originally planned noninferiority margin of 1.10 (requiring 4,700 events) would not be achievable with 90 % power unless follow-up was extended by several years or sample size increased by several thousand patients. Neither of these options seemed feasible. The committee thus considered either reducing the power to detect noninferiority, or increasing the noninferiority margin. After discussion, the committee agreed unanimously (one vote per trial) to amend the target noninferiority margin to 1.12 while retaining 90 % power to declare noninferiority with the 1.12 margin. The resulting number of events required will be 3,400 (reduced from 4,700 in the original plan). The noninferiority margin of HR=1.12 is equivalent to a three-year absolute DFS difference of 2.7 % (from 72 %

**Table 2** Disease-free survival at three and five years for stage III colon cancer treated with oxaliplatin-based chemotherapy according to recently reported studies

Trial	Regimen (treatment group)	DFS at three years (%)	DFS at five years (%)
MOSAIC [1, 2•]	FOLFOX4 (experimental)	72.2	66.4
NSABP C-07 [3, 4•]	FLOX (experimental)	NE	64.4
NO16968 [5•, 6]	XELOX (experimental)	70.9	66.1
NSABP C-08 [13•]	mFOLFOX6 (control)	72	NE
AVANT [17]	FOLFOX4 (control)	76	NE
NCCTG [16]	mFOLFOX6 (control)	75	NE
PETACC8 Intergroup [18]	FOLFOX4 (control)	78	NE

NE, not evaluated

to 69.3 %) whereas the previous margin corresponded to a difference of 2.3 % (72 % vs. 69.7 %). This new number of events (3,400) seems feasible with two years minimum follow-up on all patients, resulting in a final analysis most likely in late 2015 or early 2016.

### Modification of interim analysis plan

As originally stated, two interim analyses, after 50 % and 75 % of events, to look for futility to declare noninferiority were to be performed. The committee considered moving the analysis schedule ahead to perform the interim analyses after 33 % and 66 % of events. After discussion, this change was not recommended (vote 5–0 with one abstention) because of the feeling that a boundary at 33 % of events would be too conservative to be useful. Furthermore, the committee considered a proposal to drop the second planned interim analysis after 75 % of events. After discussion, this proposal was adopted by a vote of 4–2, on the basis of the assumption that when 75 % of events are expected to occur, all trials are expected to be already closed to accrual. This proposal will also preserve additional type I error for the final analysis.

### Accrual Update (February 2013)

Six trials are in progress, with one planned to close to inclusion in March 2013 (TOSCA trial) and five continuing inclusion (Table 3).

### SCOT trial

*EudraCT Number:* 2007-003957-10

*ClinicalTrials.gov Identifier:* NCT00749450

*Sponsor:* NHS Greater Glasgow and Clyde (UK)

*Groups:* the CACTUS and OCTO

*Chemotherapy (regimen):* XELOX or mFOLFOX6

*Activation date:* March 27, 2008

*Planned closure:* November 2013

*Current status:* open in the UK, Australia, Denmark, Spain, Sweden, and New Zealand

*Planned accrual:* 9,500 patients stage II and III (original)—4,000 stage III (revised); sites open: 159 centers open in the UK, 32 in Australia, 7 in Denmark, 19 in Spain, 11 in Sweden, and 4 in New Zealand

*Current accrual:* 4,919 patients randomized (approximately 67 percent of patients with stage III colon cancer); current accrual rate is 136 per month

*Sources of funding:* Medical Research Council (MRC) (UK) (ref: G0601705).

<http://clinicaltrials.gov/ct2/show/NCT00749450>

### TOSCA trial

*EudraCT Number:* 2007-000354-31

*ClinicalTrials.gov Identifier:* NCT00646607.

*Sponsor:* Fondazione Gruppo Italiano per lo Studio dei Carcinomi dell'Apparato Digerente (GISCAD)

*Groups:* APRIC (Associazione Per la Ricerca Clinica); GIRCG (Gruppo Italiano Ricerca Cancro Gastrico);

**Table 3** Update on patient accrual into the IDEA trial (updated at the end of February 2013)

Trial site	Trial	Group	Current (stage III)	Planned accrual
UK, Australia, Denmark, Spain, Sweden, New Zealand	SCOT	CACTUS, OCTO	3,295	4,000
Italy	TOSCA	GISCAD*	2,389	2,500
France	IDEA	GERCOR, PRODIGE (FFCD – Unicancer)	1,479	2,000
US	80702	CALGB/SWOG	972	2,500
Greece	HORG	HORG	432	1,000
Japan	ACHIEVE	JFMC	230	1,200
Total	6 trials	16 groups	8,797	≥10,500

SCOT, Short Course Oncology Treatment; TOSCA, Three or Six Colon Adjuvant; IDEA, International Duration Evaluation of Adjuvant Chemotherapy; CLEAR, Celecoxib and Length of Adjuvant Rx; HORG, Hellenic Oncology Research Group; ACHIEVE, Adjuvant Chemotherapy for colon cancer with High Evidence; CACTUS, Cancer Clinical Trials Unit Scotland; OCTO, Oncology Clinical Trials Office, APRIC, Associazione Per la Ricerca Clinica; GIRCG, Gruppo Italiano Ricerca Cancro Gastrico; \*GISCAD and collaborating groups, Gruppo Italiano per lo Studio dei Carcinomi dell'Apparato Digerente; GOAM, Gruppo Oncologico Aree Metropolitane; GOCSI, Gruppo Oncologico del Centro Sud e Isole; GOCCI, Gruppo Oncologico Chirurgico Cooperativo Italiano; GOIRC, Gruppo Oncologico Italiano di Ricerca Clinica; GOIM, Gruppo Oncologico Italia Meridionale; GONO, Gruppo Oncologico del Nord Ovest; IOR, Istituto Oncologico Romagnolo; ITMO, Italian Trials in Medical Oncology; SICO, Southern Italy Cooperative Oncology Group; SICO, Southern Italy Cooperative Oncology Group; GERCOR, Groupe Coopérateur Multidisciplinaire en Oncologie; PRODIGE, Partenariat de recherche en oncologie digestive; FFCD, Fédération Francophone de Cancérologie Digestive; CALGB, Cancer and Leukemia Group B; SWOG, Southwest Oncology Group; JFMC, Japanese Foundation for Multidisciplinary Treatment of Cancer



GISCAD; GOAM (Gruppo Oncologico Aree Metropolitane); GOCSI (Gruppo Oncologico del Centro Sud e Isole); GOCCI (Gruppo Oncologico Chirurgico Cooperativo Italiano); GOIRC (Gruppo Oncologico Italiano di Ricerca Clinica); GOIM (Gruppo Oncologico Italia Meridionale); GONO (Gruppo Oncologico del Nord Ovest); IOR (Istituto Oncologico Romagnolo); ITMO (Italian Trials in Medical Oncology); SICOOG (Southern Italy Cooperative Oncology Group)

Chemotherapy (regimen): FOLFOX4

Activation date: June 20, 2007

Planned closure: December 2012

Current status: closed in March 2013

Sites open: 130 sites; current accrual: 3,759 patients (2,389 patients with stage III colon cancer)

Sources of funding: Italian Ministry of Health

<http://clinicaltrials.gov/show/NCT00646607>

## IDEA France

EudraCT Number: 2009-010384-16

ClinicalTrials.gov Identifier: NCT00958737

Sponsor: GERCOR

Groups: PRODIGE (FFCD – FNCLCC) and GERCOR

Chemotherapy (regimen): XELOX or mFOLFOX6

Activation date: May 2, 2009

Current status: open; planned accrual: 2,000 patients; sites open: 135 open centers; 122 centers enrolled at least one patient; current accrual: 1,479 patients randomized (all patients with stage III colon cancer); accrual rate is approximately 45 patients per month

Sources of funding: PHRC National Cancer 2009 and Institut National du cancer (French National Cancer Institute)

Others: Tissue and blood collection is ongoing

<http://clinicaltrials.gov/ct2/show/NCT00958737?term=idea&rank=3>

## CALGB/SWOG Colon Trial C80702

ClinicalTrials.gov Identifier: NCT01150045

Sponsor: CALGB

Groups: SWOG and CALGB

Chemotherapy (regimen): mFOLFOX6

Activation date: July 2010

Current status: open

Planned accrual: 2,500 patients

Sites open: 588 sites are listed in ClinicalTrials.gov – endorsed by all adult oncology treatment cooperative groups in the US and Canada

Current accrual: 972 patients with stage III, current accrual rate is 45 patients per month

Sources of funding: Cancer Therapy Evaluation Program (CTEP) by National Cancer Institute; Pfizer Oncology is providing celecoxib and placebo.

<http://clinicaltrials.gov/ct2/show/NCT01150045?term=celecoxib&rank=91>

## HORG trial

ClinicalTrials.gov Identifier: NCT01308086

Sponsor and Group: HORG group

Chemotherapy (regimen): XELOX or FOLFOX4

Activation date: October 2010

Current status: open;

Planned accrual: 1,000 patients

Sites open: 15 sites have been activated (15 have at least one patient enrolled)

Current accrual: 569 patients (382 patients with stage III cancer); accrual rate is 33 patients per month for last three months

Sources of funding: HORG group.

## ACHIEVE trial, JFMC 47-1202-C3

UMIN-CTR Clinical Trial Identifier: UMIN000008543

Sponsor and Groups: Japanese Foundation for Multidisciplinary Treatment of Cancer (JFMC)

Chemotherapy (regimen): XELOX or mFOLFOX6

Activation date: August 1, 2012

Current status: open

Planned accrual: 1,200 patients; target accrual is 50 patients per month once all sites are open; Sites open: 52 sites open, goal is to have 440 total sites

Current accrual: 230 patients with stage III colon cancer

Sources of funding: JFMC under contract with Yakult Honsha

<https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=browses&action=browses&type=summary&recptno=R000010043&language=E>

The total accrual in February 2013 for the six IDEA trials reached 8797 patients. A sample size of 10,500 patients is projected by the end of 2013. Given that accrual extending beyond the planned accrual will lead to higher number of DFS events and will enable earlier definitive analysis, all trials are encouraged to continue accrual as long as possible.

## Discussion and Conclusions

The IDEA collaboration is a new model for international collaboration with six trials accruing patients and combined accrual, as of February 2013, surpassing 8,500 stage III

colon cancer patients. Five of the six trials within the IDEA collaboration are actively accruing patients (Table 2) with worldwide accrual continuing to exceed 250 patients per month. If all trials continue at their current pace, the collaboration remains on track to achieve and probably exceed the accrual objective of 10,500 patients before the end of 2013.

The IDEA collaboration is a unique example of academic international collaboration, with the objective of reducing treatment duration, toxicity, and cost of adjuvant therapy in colon cancer. Conventional chemotherapy is administered for six months and is associated with a clinically relevant risk of long-term neurotoxicity. Therefore, the type of study proposed here is extremely important for improving the quality of life of patients who suffer from colorectal cancer. One major issue of the IDEA collaboration is to reduce cumulative, potential long-lasting neuropathy. In the MOSAIC study, 48 months after the end of chemotherapy, grade 1, 2, and 3 peripheral sensory neuropathy was observed in 11.9 %, 2.8 %, and 0.7 % of the patients examined, respectively. A reduction of adjuvant chemotherapy to less than six months has proved effective for other cancers, for example breast and testicular cancer, and was better tolerated by patients in clinical practice [14, 15]. The question about optimum duration of adjuvant therapy in breast cancer was recently addressed in the Cancer and Leukemia Group B (CALGB) 40101 phase III trial [14]. The CALGB 40101 trial enrolled 3,171 women with operable primary breast cancer and zero to three positive nodes between 2002 and 2008. Patients were randomized to receive doxorubicin and cyclophosphamide (four or six cycles) or paclitaxel (four or six cycles). Multivariate proportional hazards modeling showed that six cycles of treatment was not superior to four cycles for either relapse-free or OS after adjustment for tumor size, number of positive nodes, hormone receptor status, and menopausal status. Not unexpectedly, more toxicity was observed with six cycles of therapy. This crucial study confirmed that shorter duration of chemotherapy for early stage breast cancer should be considered as standard of care [14].

Targeted therapy has been developed as single-agent chemotherapy, but a target is part of a complex network of interactions with multiple targets [13•, 16–18]. Recent studies indicate that adjuvant use of targeted therapy may not involve chemotherapy, at least in the context of currently available targeted therapy (bevacizumab or cetuximab). However, it might be possible to study sequential treatment, for example chemotherapy followed by targeted therapy.

FOLFOX4 was administered only in the TOSCA and HORG trials. In the four other studies, only two regimens were used, mFOLFOX6 and XELOX. mFOLFOX6 was preferred to the validated FOLFOX4 regimen, because the mFOLFOX6 regimen is more convenient than FOLFOX4

for the patient and less expensive: one day vs. two days in the out-patient unit without evidence of further toxicity resulting from the increased dose of 5-FU. No study has directly compared FOLFOX4 with mFOLFOX6 in an adjuvant setting. However the three-year DFS in the standard group (mFOLFOX6) of the NSABP C-08 study and the NCCTG study N0147 was at least comparable with that observed in patients treated with FOLFOX4 in the MOSAIC and AVANT studies (Table 2) [1, 2•, 13•, 16–18].

The IDEA Steering Committee and gastrointestinal investigators worldwide are clearly committed to providing a definitive answer to the primary IDEA hypothesis that three months of FOLFOX or XELOX therapy is non-inferior to the standard six-month regimen. The IDEA Steering Committee wishes to sincerely thank all IDEA investigators, staff, and most importantly, patients, who are contributing to this international effort. IDEA's success is a testimony to the outstanding collaborative nature of gastrointestinal cancer investigators worldwide.

#### Compliance with Ethics Guidelines

**Conflict of Interest** Thierry André has received compensation from Roche and Sanofi for service as a consultant, and payment for lectures including service on speakers bureaus from Roche. Timothy Iveson has received compensation from Roche for service as a consultant and payment for lectures including service on speakers bureaus, and has received reimbursement from Roche, Amgen, and Sanofi for travel to conferences. Roberto Labianca, Jeffrey A. Meyerhardt, and Ioannis Souglakos declare that they have no conflict of interest. Takayuki Yoshino has received a consulting fee/honorarium from Chugai and Yakult; has received compensation from Takeda for service as a consultant; is supported by grants from Daiichi Sankyo, Taiho, Bayer, and ImClone; has received payment for lectures including service on speakers bureaus from Chugai, Yakult, Bristol-Myers Squibb, and Merck Serono. James Paul is supported by a grant from the National Institute for Health Research (NIHR)/Medical Research Council (MRC) EMR Programme. Alberto Sobrero has received compensation from Sanofi, Amgen, Bayer, and Roche for service as a board member and a consultant. Julien Taieb has received compensation from Roche, Merck, and Sanofi for service as a board member and payment for lectures including service on speakers bureaus, and is supported by grants from Roche, Merck, and Sanofi. Anthony F. Shields is supported by a grant from Southwest Oncology Group (SWOG)/National Cancer Institute (NCI) (Grant #U10 CA032102). Atsushi Ohtsu declares that he has no conflict of interest. Axel Grothey has received a consulting fee/honorarium from Sanofi, and has received compensation from Genentech, Bayer, and Amgen for service as a consultant. Daniel J. Sargent is supported by a grant from the Mayo Clinic.

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- Of importance
- Of major importance

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